International Journal of Dermatology

Review

Food allergy update: more than a peanut of a problem

Zain Husain, MD, and Robert A. Schwartz, MD, MPH

Dermatology and Pathology, New Jersey Medical School, Newark, NJ, USA

Correspondence
Dr. Robert.A. Schwartz, MD, MPH
Dermatology
New Jersey Medical School
185 South Orange Avenue
Newark
NJ 07103-2714
USA
E-mail: roschwar@umdnj.edu

Conflicts of interest: None.

Abstract

Food allergies have become a significant medical and legal concern for children worldwide, as there is a rising incidence of potentially fatal hypersensitivity reactions. The most common foods implicated include cow milk, wheat, egg, soy, peanut, tree nuts such as walnuts, hazelnuts, almonds, cashews, pecans, and pistachios, fish and shellfish. The majority of food allergies represent an IgE-mediated hypersensitivity reaction to specific proteins found in foods. Peanut allergy, in particular, is a significant food allergy responsible for the majority of patients with food-induced anaphylaxis. Even trace quantities to food proteins in the sensitized individual can lead to fatal reactions. There is often a rapid onset of symptoms after exposure, with prominent cutaneous findings of urticaria, angioedema, or diffuse nonspecific dermatitis. The majority of children outgrow allergies to milk, soy, egg, and wheat. However, allergy to peanuts, tree nuts, and seafood are usually lifelong conditions, as few outgrow it. Children with food allergies and their families should be knowledgeable of management strategies for the condition, including carrying and properly administering self-injectable epinephrine. New immunotherapeutic options are being investigated and appear promising.

Introduction

Food allergies are common, affecting 6–8% of children younger than four years old and 4% of the US population older than 10 years old.[1–3] Peanut, cow milk, wheat, egg, soy, tree nuts such as walnuts, hazelnuts, almonds, cashews, pecans, and pistachios, fish and shellfish are responsible for the majority of clinical reactions.[4] Peanut allergy is common and severe, representing the majority of food-induced anaphylaxis cases.[5–8] It has garnered significant attention in the media, as its prevalence is increasing, and exposure to even trace quantities of peanuts in the sensitized individual can lead to fatal reactions. Likewise, it appears that the prevalence of all food allergies is increasing. These allergies arise from an IgE-mediated hypersensitivity reaction to proteins found in these foods with rapid onset of clinical features, including cutaneous, gastrointestinal, and respiratory manifestations.[1] Skin prick tests and food-specific IgE measurements are diagnostic tests that can be useful in lieu of potentially dangerous oral food challenges. These allergies generally begin in childhood. Most individuals outgrow them, particularly those to milk, soy, egg, and wheat.[9–11] However, peanut, tree nut, and seafood allergies are usually lifelong conditions, with only few individuals outgrowing them.[12] New treatments, particularly in immunotherapy, are being investigated.

Prevalence

Food allergies have been increasing significantly worldwide in the past 10 years. This may be attributed in part to reactions to exotic and ethnic ingredients being increasingly used in food preparation.[1] Another possibility may be due to increased exposure to food products found in nonedible manufactured goods.[1] There is wide variation in the prevalence of food allergy among studies because data collection methods are not standardized. One study estimated that food allergies affect 6–8% of children younger than four years old and 4% of the US population older than 10 years. [1–3] A double-blind placebo controlled challenge has demonstrated that the prevalence of IgE-mediated food allergy varies between 2 and 5% in adults; children <3 years old had an overall prevalence rate of 6%.[13] A prospective birth cohort study demonstrated a prevalence of 3.2–4% confirmed by challenges.[14] Food allergy usually manifests in infancy and peaks at one year of age and declines after three - years. In children, over 80% of reactions are due to milk, egg, soy, wheat, peanut, and tree nuts whereas in adults most are due to peanuts, tree nuts, shellfish, and fish.[15]

Pathophysiology

Food allergies are IgE-mediated hypersensitivities to specific proteins found in the food.[1] In susceptible indi-

viduals, sensitizing exposure leads to the production of the protein-specific IgE, which are then bound to high-affinity IgE receptors on mast cells or basophils. Re-exposure to the food allergen causes adjacent cell-bound IgE and peanut allergen to cross-link, causing degranulation of preformed inflammatory mediators such as histamine, prostaglandins, and leukotrienes. Interleukin (IL) 4 and IL-13, cytokines, and chemokines are also produced during this process, which recruits other inflammatory cells. The result of these reactions manifests as clinical symptoms of allergy and anaphylaxis.[4]

The development of allergies to food proteins depends on protein structure, dose of allergen, and genetic susceptibility of the host. Sensitization can occur through three primary routes: gastrointestinal tract (class I allergens), respiratory tract (class II allergens), and epicutaneously.[16] In general, class I allergens are heat stable, and acid and proteolysis resistant, and commonly induce allergy in children. Children are frequently sensitized to class I allergens such as cow milk proteins (casein, whey), egg (ovalbumin, ovomucoid), peanut (vicillin, conglutin, glycinin), shellfish (tropomysin), and fish (parvalbumin).[15] Class II allergens frequently affect adults, as they inhale plant and tree pollens.

Plant food allergens are often classified based on their structural and biological properties.[15] Conformational or sequential epitopes are responsible for immunogenicity of proteins. Heating or enzymatic action can lead to changes in tertiary structure of the protein, giving rise to conformational epitopes. In contrast, sequential epitopes are resistant to processing and are involved in more severe and permanent allergic responses.

Foods with cross-reacting epitopes can also lead to IgE-mediated clinical responses. Foods that are derived from a common phylogenetic lineage often have proteins similar in structure. For instance, there is a great degree of cross-reactivity between peanuts and other legumes and tree nuts. As a member of the legume family, peanuts share homologous proteins with peas, beans, carob beans, kidney beans, garbanzo beans, clover, lupines, and lentils.[17] Individuals with clinical reactions to a single legume (38–79%) show IgE binding (positive skin test/RAST) to a variety of legumes.[18] In another study using oral food challenge, 5% of patients with peanut allergy had a positive challenge to more than one legume.[18] There is significant cross-reactivity between peanuts and tree nuts, with one study showing 2.5% of patients having allergy to both.[19] In a study of 142 patients with peanut allergy, Moneret-Vautrin *et al.*[5] found that 50% were sensitized by skin prick testing to almonds, 40% to cashews, 30% to pistachios, 26% to Brazil nuts, and 21% to hazelnuts.

Clinical features

Clinical symptoms of food allergy range significantly in severity and presentation from mild urticaria and pruritus to frank, potentially life-threatening anaphylaxis. Reactions may appear within seconds and up to two hours following ingestion of the food allergen.[1] Even trace quantities can give rise to the IgE-mediated reactions affecting the cutaneous, cardiovascular, gastrointestinal, and respiratory systems (Tables 1 and 2).[20] Symptoms include pruritic erythematous rash, urticaria, angioedema, wheezing, nausea, and vomiting. In severe cases, anaphylaxis can present with associated abnormalities such as hypotension and dysrhythmia.

Peanut allergy

Peanuts are native to South America and have been cultivated there since 2000–3000 BC.[21] They were brought to Europe under the Spanish Empire and quickly spread throughout the world. They have since become a common food in many countries, including the USA. Peanuts are valued because they serve as a source of easily digested protein and have extensive food and industrial applications such as the manufacturing of plastics, linoleum, adhesives, bleaches, and shampoos.

Peanut allergy is one of the most commonly studied food allergies, with its prevalence followed closely. In 1997, 0.6% of the US population reported allergy to peanuts and tree nuts, which rose to 1.1% in 2002, due to an increase in peanut allergy prevalence among young children from 0.4% to 0.8%.[3] In another study, Tariq *et al.*[22] followed a cohort of 3 and 4–year-old children born between 1994 and 1996 and another cohort born in 1989 from the Isle of Wight, UK. There was a two-fold increase in reported peanut allergy (0.5–1%) and three-fold increase in sensitization (1.1–3.3%). The prevalence of peanut allergy was estimated to be 1.5% in the 1994–1996 cohort after oral food challenges. In a nationwide cross-sectional random digit dial telephone survey, 0.4% of children and 0.7% of adults were reported to have peanut allergy.[3] The estimated prevalence of peanut allergy in developed countries is between 0.6% and 1.0%.[12]

The cause of the increasing prevalence of peanut allergy has not been fully elucidated. Several theories have been proposed to explain this recent trend. One theory, which

Table 1 Cutaneous manifestations of peanut allergy

Urticaria
Angioedema
Pruritic erythematous rash

Table 2 Extracutaneous manifestations of peanut allergy

Gastrointestinal
Vomiting
Abdominal pain
Diarrhea
Respiratory
Coughing
Laryngeal edema
Voice change
Wheezing
Anaphylaxis (in addition to cutaneous and above symptoms)
Hypotension
Dysrhythmia

applies to increasing prevalence of all allergies, is the hygiene hypothesis. It claims that decreased exposure to specific viral infections and endotoxins during early life is leading to increased allergies.[23] Maternal ingestion of peanuts during pregnancy and lactation and the timing of peanut introduction to an infant or child has also been examined.[1] In one study, many infants younger than four months old had positive skin tests to peanut, which was thought to be due to exposure *in utero* or breast milk.[5] Furthermore, many individuals with peanut allergies were found to have been breast-fed for the first several months of life.[24] Increased peanut consumption, use of peanut containing nonfood products, early introduction of potentially cross-reacting proteins such as soy or carob, and processing techniques may be responsible for increasing prevalence of this allergy.[18,24–27]

Proteins of the peanut cotyledon are the primary allergens.[4] There are eight peanut allergens identified to date, Ara h1–Ara h8. They are named after the scientific name for the legume, *Arachis hypogaea*.[28–33] Ara h1 and 2 are the major peanut allergens and are classified as storage proteins. Over 90% of peanut allergic patients have IgE antibodies to these proteins individually, whereas 45–95% have IgE antibodies to Ara h3.[4] Overlapping peptides and serum peanut-specific IgE from patients with documented peanut hypersensitivity have been used to map the linear IgE-binding epitopes of the major peanut allergens. These epitopes are resistant to acid, heat, and enzymatic degradation. However, food-processing techniques can lead to modifications, as seen with dry roasting, which increases allergenicity when compared with boiling and frying peanuts.[34] Roasting leads to the Maillard reaction, which results in glycosylation of amino groups to form stable advanced glycation end-products.[17] In one study, roasted peanuts were found to have 22-fold higher extractable Ara h1 compared with raw peanuts.[17]

Clinical symptoms of peanut allergy can develop rapidly and are potentially life threatening. Over 95% of reactions occur within 20 minutes of peanut ingestion.[4] Small quantities of peanut proteins can induce subjective and objective symptoms, far less than that found in a typical peanut (200 mg of protein).[35] In a survey of members of a voluntary national peanut/tree nut allergy registry,[6] the average age of diagnosis was 14 months with symptoms occurring after the first known peanut ingestion in 75% of those children eating peanuts for the first time. Symptoms usually manifested within three minutes. Patients were exposed to the allergen through ingestion (91%), presumed skin contact (8%), and inhalation (1%). An unusual clinical feature of peanut allergy is the possibility of biphasic reactions, in which allergic symptoms recur 1–8 hours after the initial symptoms have resolved.[12] Individuals with life-threatening reactions are usually adolescents or adults and usually have asthma or a history of atopy. It is rare to have fatal reactions occur after first ingestion.[1]

Peanut allergy frequently involves multiple organ systems.[20,36] In one study, two organ systems were affected in 31% of initial reactions, whereas three systems were affected in 21%.[24] A French study showed that clinical symptoms due to peanut allergy included flare of atopic dermatitis (46%), urticaria/angioedema (32%), asthma (15%), generalized anaphylaxis (5%), and gastrointestinal symptoms (3%).[20] Nearly all allergic reactions involved the skin (89%), with cutaneous symptoms ranging from acute urticaria, angioedema, and a pruritic erythematous skin rash.[20] Isolated skin manifestations occurred uncommonly. In such cases, patients had lower serum peanut-specific IgE levels (1.25 kUA/l) than the group with extracutaneous symptoms (11.65 kUA/l).[37] Fifty-two percent of patients exhibited upper and lower respiratory tract symptoms, including laryngeal edema, repetitive coughing, voice changes, and wheezing.[24] Gastrointestinal symptoms were seen in 34% of cases and included acute vomiting, abdominal pain, or diarrhea.[24] The most severe manifestation, anaphylactic reaction, included the previously mentioned symptoms as well as cardiovascular abnormalities such as hypotension and dysrhythmia.

Tree nut allergy

Tree nuts are another considerable source of food allergy similar to that of peanuts. The 12 major types of edible tree nuts grown include almonds, English (or Persian) walnuts, pecans, cashews, pistachios, hazelnuts (filberts), Brazil nuts, macadamia nuts, pine nuts (piñon nuts, pignolias), chestnuts, black walnuts, and coconuts.[38] According to a survey on tree nuts and peanut allergy, the prevalence of tree nut allergies is 0.5% in the USA.[3] Most tree nut allergens identified to date are seed storage proteins such as the vicilins, legumins, and albumins.[39] Most reactions occurred on first exposure, and two-thirds

had more than five reactions. Many patients had reactions to more than one tree nut. One study showed that the tree nuts most commonly implicated in allergy include cashew, walnut, and pecan.[40] Another survey of 54 confirmed tree nut allergic pediatric patients showed that walnut was the leading allergic-response tree nut (26% of patients), followed by almond (13%), pecan (13%), cashew (11%), hazelnut (7%), pine nut (7%), pistachio (7%), and Brazil nut (4%).[24] There was significant cross-reactivity between tree nuts, and molecular studies have shown homology among the seed storage proteins. Similar to peanuts, tree nut allergies are usually life long, but some outgrow it. A study done at a tertiary allergy referral center showed that 9% of patients outgrew their tree nut allergies.[40] Therefore, patients with this particular allergy should be re-evaluated for tolerance. Patients with tree nut-specific IgE below 5 kUA/l should be considered for a challenge. There is extensive cross-reactivity between different tree nuts, so avoidance of all nuts should be advocated in the tree nut allergic patient.

Milk allergy

Milk allergy is common among infants and young children. The prevalence rate is estimated to be 2.5%.[15] Clinically, symptoms range from IgE immediate reactions such as urticaria and angioedema to life-threatening anaphylaxis. There can also be non-IgE-mediated reactions such as atopic dermatitis or eosinophilic gastrointestinal disorders. A Danish study showed that 2.2% of infant subjects had proven cow milk allergy.[41] Among those with allergy, 64% showed cutaneous symptoms, 59% gastrointestinal symptoms, and 33% had respiratory symptoms. The primary allergen in cow milk is casein, followed by whey protein. Children usually develop tolerance to milk by age 3–5 years in up to 85% of children.[41] Patients may be able to tolerate small amounts of milk found in baked goods and other foods. There is also significant cross-reactivity between cow milk and goat or sheep milk, estimated to be 90%.[42] However, there is only 4% cross-reactivity between cow milk and mare milk.[43] Most children can tolerate soy-based formula, but it is generally not recommended because it may lead to development of allergies to other foods in infants at risk of developing food allergies.[15] Extensively hydrolyzed milk-based formulas are tolerated by almost all infants with cow milk allergy and are an acceptable alternative.[15]

Egg allergy

Egg allergy is also another common pediatric food allergy. The prevalence rate for this condition is 2.5%.[13] Clinical manifestations include urticaria, atopic dermatitis, and in severe cases, anaphylaxis. Eggs are commonly found in baked goods and a variety of other dishes, making avoidance difficult. The major allergens found in eggs include ovomucoid (the primary allergen), ovalbumin, ovotransferrin, and lysozyme. Children usually develop tolerance to egg by five years of age. They often tolerate regular ingestion of small quantities of cooked egg in baked products, which may hasten tolerance development.[44] Influenza vaccination of egg-allergic patients is a common topic of discussion and remains controversial. It is currently not recommended to immunize patients with previous significant reactions or anaphylaxis to egg.[44]

Cereal grain allergy

Cereal grains are another common food allergen in the pediatric population, which include wheat, maize (corn), rice, barley, sorghum, oats, millet, and rye. Allergy to wheat is one of the most common among cereal grains and the most extensively studied. In a population-based birth cohort (Barn Allergi Miljö Stockholm Epidemiologi Projektet, BAMSE) in Stockholm, the prevalence of wheat sensitization was 4% among 2336 4-year-old children.[45,46] Zuidmeer *et al.*[47] reviewed two population-based studies from the UK and one from Germany, which reported positive wheat challenge tests in children, with prevalence as high as 0.5%. Allergens found in cereal grain include proteins such as albumins, globulins, prolamins, and glutenins.[48] Clinical responses include acute IgE-mediated reactions of immediate onset, urticaria, angioedema, bronchial obstruction, nausea, and abdominal pain, or in severe cases systemic anaphylaxis.[49] There are also uncommon reactions, such as the wheat-induced exercise-mediated acute allergic response, and cell-mediated reactions, such as atopic dermatitis, gastrointestinal manifestations, and celiac disease. Although sensitization occurs primarily through ingestion, inhalation is another route well described in bakers who develop occupational asthma.[15] Hydrolyzed wheat protein is also an additive to many topical cosmetic formulations, another possible route of wheat sensitization that needs further investigation.[1] Patients with wheat allergy can usually tolerate other grains. Jones *et al.*[50] evaluated the cross-reactivity among cereal grains and related grass to determine the prevalence of multigrain hypersensitivity. Results from this study showed that 21% of patients had symptomatic reactivity from oral food challenge, and 80% had reactivity to only one grain. Cross-reactivity among the cereal grains and grasses was clinically insignificant in most cases. Wheat allergy usually begins in early childhood and is outgrown by 3–5 years of age in most cases.[49] Most wheat-allergic children also suffer from moderate-to-severe atopic dermatitis and sensitization to other foods such as milk and eggs.[49]

Fish and seafood allergy

Allergy to fish and crustaceans, such as shrimp, lobster, crab, and crawfish, is also common, particularly in the adult population. A nationwide, random cross-sectional telephone survey of over 5000 households in the USA was conducted to determine prevalence of fish or shellfish allergy.[51] Results among participants showed a prevalence of 2.3% for any seafood allergy, 2% for shellfish, 0.4% for fish, and 0.2% for both types. This allergy was more common in adults than in children. Clinical features from this study showed that half of this population reported dyspnea and throat tightening, and about 60% reported recurrent reactions. In individuals with seafood allergy, the rate of reactions to multiple fish was 67%, whereas 38% of patients react to more than one crustacean and 49% react to multiple mollusks. In addition to typical IgE-mediated reactions, there can also be delayed gastrointestinal reactions to oysters and clams. There are reported cases of occupational asthma and contact urticaria from handling seafood.[15] The major allergen in fish is parvalbumin, which is highly resistant to heating and digestive enzymes, whereas tropomysin is the primary allergen in crustaceans.[15] The majority of seafood allergies are lifelong. There is significant cross-reactivity between different species of fish, including freshwater and saltwater fish, as well as between crustaceans. However, there is no cross-reactivity between crustaceans and fish. It is worth mentioning that histamine fish poisoning, a condition with several similar clinical features to fish allergy, is not a true allergy. This condition follows ingestion of fish containing toxic tissue levels of histamine. This is secondary to bacterial overgrowth from poor refrigeration and subsequent enzymatic conversion of histadine-to-histamine. Patients present with facial flushing, nausea, diarrhea, dizziness, and cramps and are treated with supportive therapy and antihistamines.[15]

Vegetable and fruit allergy

Fruit and vegetables are another source of common food allergy, which commonly manifests as the oral allergy syndrome (OAS). OAS is a reaction characterized by oropharyngeal pruritus, tingling, and/or edema that develops after eating specific fresh fruits and vegetables.[15] Peaches, nectarines, and members of the Rosaceae family are common fruits associated with OAS.[15] The condition is rarely life-threatening and usually resolves without treatment. Cooking or peeling the fruit usually prevents reactions, as the allergen is likely concentrated in the peel and is usually heat labile.[15] The main allergens believed to cause this reaction are lipid transfer proteins, with thaumatin-like proteins also involved in some reactions. There is little cross-reactivity between fruits and vegetables. In contrast, there is significant reactivity between pollens and fruits/vegetables. In an Italian study, Pastorello *et al.*[52] have shown a high prevalence of OAS in pollinosic patients and consider hayfever as the major risk factor for OAS to vegetables and fruits. In particular, birch pollinosis is associated with allergy to apple, pear, and other Rosaceae fruits as well as to Umbelliferae vegetables such as celery, fennel, and carrots.[52] Other common cross-reactions include ragweed allergy with melon and banana allergy, birch allergy with apple allergy, and latex allergy with allergy to melons, banana, kiwi, avocado, and chestnut.[53]

Seed allergies

Seed allergies are also increasing in prevalence throughout the world. Common seeds include mustard, poppy, sunflower, cottonseed, dill, coriander, flaxseed, caraway, sesame, fennel, and anise. These allergies are common in Israel and the Middle East, where consumption is high.[54] The allergens responsible for these reactions are seed storage proteins, which are generally stable and heat resistant.[15] Agne *et al.*[55] conducted a study of sesame seed allergy in 14 children recruited from three allergy centers in France. Their results showed that the median age of onset of sesame seed allergy was five years. All of the patients reacted immediately after ingestion of sesame seeds. Clinical manifestations included edema (nine cases, 48%), urticaria (five cases, 27%), and one of each of the following symptoms: vomiting, rhinitis, conjunctivitis, asthma, and anaphylactic shock. Two patients, who were both asthmatics, suffered anaphylactic shock. The patients were followed up between a few months to six years, during which three patients outgrew their sesame seed allergy.

Diagnosis

Identifying a particular food as the cause of a food allergy requires a detailed history and physical examination. It is essential to determine the temporal association between ingestion and symptoms, type of symptoms, amount ingested, and symptoms after eating similar foods. Dietary diaries can be helpful. Personal or family history of atopy is also worth investigating, as it is commonly seen in patients with food allergy. Skin prick test (SPT) or fluoroenzyme immunoassay (ImmunoCAP-FEIA) can help with diagnosis by detecting food-specific IgE (Table 3).[4] SPT is performed with a commercially available protein extract, which is convenient, inexpensive, and rapidly interpretable. This simple diagnostic test is commonly used in the detection of peanut allergy. For example, in peanut-specific SPT, a wheal 3 mm greater than the negative control is considered a positive reaction, and a wheal

Table 3 Diagnostic testing

Test	Criteria	Advantages	Disadvantages
Skin prick testing	wheal 3 mm > negative control or wheal > 8 mm	Convenient Inexpensive Rapidly interpretable Negative predictive value(>95%) Low risk of reaction	Specificity (30–60%) Positive predictive value (<50%)
ImmunoCAP-FEIA	IgE > 15 kUA/l	Positive predictive value (95%) No risk of reaction	Expensive Limited laboratory availability Lack of age-specific norms
Oral food challenge	Clinical reaction	Gold standard	High risk of severe reaction Time consuming

larger than 8 mm is likely to predict clinical reactivity.[56,57] SPTs yield excellent negative predictive values (>95%) but poor specificity (30–60%) and positive predictive value (<50%). Serious reactions to SPT are extremely rare and have occurred primarily in patients with active wheezing.[12]

The ImmunoCAP-FEIA assay semiquantitatively measures allergen-specific IgE bound to standardized allergen with results ranging from <0.35 to >100 kUA/l. These values correlate with probability of clinical reactivity but not severity of reaction.[12] Compared with other foods, ImmunoCAP-FEIA tests for peanuts, tree nuts, fish, shellfish, egg, and milk are better standardized and have accurate predictive values. Food-specific IgE levels and cut-off values indicating high clinical reactivity have been determined to avoid food challenges: 7 kUA/l for egg, 14 kUA/l for peanut, 15 kUA/l for milk, and 20 kUA/l for fish.[15] It has been shown that peanut-specific IgE greater than 15 kUA/l has a 95% predictive value for an allergic reaction upon peanut exposure.[58] The ImmunoCAP-FEIA test is particularly useful for patients in whom antihistamines cannot be withdrawn for skin testing or if severe skin conditions prohibit testing. The disadvantages of this *in-vitro* assay include expense, delayed results, limited availability of approved laboratories, and lack of age-specific norms. Double-blinded, placebo-controlled oral food challenge remains the gold standard for diagnosing any food allergy (Table 3).[12] These tests are generally performed when the skin tests and food-specific IgE tests are negative and the patient still complains of symptoms associated with a particular food or if there was anaphylaxis on initial exposure. In oral food challenges, signs and symptoms of reaction are recorded before each dose. When a reaction does occur, the challenge is stopped and treatment immediately provided. The patient usually ingests incremental portions of food or placebo at 15–30 minute intervals. Although it is the gold standard, it is time-consuming, requires close supervision by medical personnel, and is dangerous, as it carries the risk of a severe reaction.[12]

Management

Management of food allergy centers on patient and family education on the allergic condition. Although there is a wide clinical spectrum of reactions, complete avoidance of the specific food responsible for the allergy should be recommended. This can be very difficult, as the food may be hidden in unexpected products and there is always a risk of cross-contamination. Patients and their families should be advised to carefully inspect food ingredient labels and ask about risk of cross-contamination at restaurants. School personnel should be informed about the child's allergy and develop a plan of action to be implemented during a reaction. In addition, patients should always wear Medic Alert bracelets, notifying others of their allergy in the case of emergency, and have a written anaphylaxis plan.[12] There are numerous resources available to patients and their families for information on various food allergies, treatments, and support.

It is essential for patients and their families to quickly recognize the early signs of allergic reactions upon accidental exposure (Table 4). Self-injectable epinephrine such as EpiPen should be prescribed. Patients and their family should be instructed on how to properly administer epinephrine in the case of emergency.[1] Risk of fatal outcomes and biphasic reactions can be reduced by injecting this drug early in the course of the reaction.[20] Anaphylaxis should be aggressively treated with intramuscular epinephrine and the patient transported to a medical facility where additional treatment can be provided such as antihistamines, oxygen, inhaled albuterol, and systemic corticosteroids.[1] A 3-day course of oral prednisone (1 mg/kg bodyweight per day) and an antihistamine should also be

Table 4 Treatment of acute food allergy reaction

• Treatment of early stages of allergic symptoms by patient or family members
Injection of epinephrine depending on patient's history and symptoms
Administration of oral antihistamine
• Transportation to emergency medical facility by emergency personnel
Airway management and supplemental oxygen
Intramuscular epinephrine
• Intravenous fluids
Oral, intramuscular, or intravenous H1-receptor antagonist
Oral prednisone or intravenous methylprednisolone
Nebulized albuterol
Possible use of H2-receptor antagonist
• Discharge instructions
Oral H1-receptor antagonist for 3 days
Oral prednisone
Follow-up with appropriate specialist

given to the patient.[1] Anaphylactic reactions may have a biphasic course that occurs 1–8 hours after onset of symptoms, including 30% of peanut anaphylaxis cases. Thus, patients should be observed under medical supervision for 4–8 hours after onset of allergic symptoms.[12]

Future prospects

New treatments for food allergy are being developed to provide patients with alternatives to current therapy. Research for treatment of peanut allergy is particularly active, as various forms of immunotherapy being investigated are likely to be applied to other food allergies in the future. Traditional injection immunotherapy has long been avoided for peanut allergy because of high incidence of serious adverse effects. In one study, patients participated in a double-blind placebo-controlled study of rush immunotherapy for treatment of peanut allergy. Patients in the treatment group tolerated increased amounts of peanuts in post-treatment food challenges than in the control group.[34] However, the high rate of serious adverse reactions in response to the therapy made it unacceptable for routine use. Blumchen *et al.*[59] showed that oral immunotherapy conducted over a longer period appears to be safer than rush immunotherapy and is effective in many patients with peanut allergy. Results showed that patients were able to tolerate a median of 1 g of peanut protein compared with 0.19 g before immunotherapy. There were mild symptoms seen in only 2.6% of doses.[59]

Peptide immunotherapy is being developed using peptide fragments containing T-cell reactive epitopes, instead of whole peanut protein, to improve patient safety. A study of a mouse model using Ara h2 peptide immunotherapy showed that pretreatment with two doses of the major peanut protein mixture before the peanut challenge has been shown to prevent anaphylactic reactions, lowered plasma histamine levels, and increased interferon-gamma production by spleen cells in peanut sensitized mice compared with controls.[23] Genetically engineered allergen proteins have also been proposed. These proteins are designed to have amino acid substitutions within IgE-binding epitopes.[23] In an *in vivo* study, mice were sensitized with whole peanut and then desensitized by intranasal administration of mutated Ara h2. Results showed suppressed synthesis of Ara h2-IgE with decreased symptoms on oral peanut challenge compared with the control group.[23] Other potential treatments include plasmid DNA-based immunotherapy and ISS-oligodeoxynucleotide-based immunotherapy. These options provide some protection from allergy but do not reverse established peanut allergy.[17,19]

Humanized anti-IgE monoclonal antibody therapy, which has been used to treat asthma and respiratory allergy,[60–63] is also being investigated for use in peanut allergy. Anti-IgE antibody binds to IgE and prevents it from binding to mast cells and basophils, precluding allergic reaction. A recent study of anti-IgE treatment in peanut allergic patients showed a significant increase in the threshold dose of peanut flour required to induce symptoms.[64] Traditional Chinese medicine has been used for the treatment of allergies for centuries and may be helpful in treating peanut allergy.[65] The herbal formula FAHF2 was used in a mouse model to determine its use in peanut allergy.[65] The control mice developed severe anaphylactic signs, decreased rectal temperatures, and increased plasma histamine levels, while those mice treated with FAHF-2 did not show signs of anaphylaxis.

Prognosis

The prognosis of food allergy varies significantly based on type of clinical response and the molecular characteristics of the causative food protein. Among children with allergy to milk, egg, soy, and wheat, 85% outgrow their allergy by three years of age.[15] However, the majority of peanut, tree nut, and seafood allergies do not resolve. Although it is not clear why certain allergies tend to resolve while others persist for life, it is likely related to the molecular complexity and antigenicity of the respective protein epitopes. The peanut allergy is usually lifelong; adults have a similar rate to that seen in children.[40] However, some individuals outgrow their allergy, as seen in one study where 18% of individuals with peanut allergy had resolved when participating in oral peanut challenges.[66] Skolnick *et al.*[67] performed an oral food challenge study with children ages 4–20 years old with serum peanut-specific IgE less than 21 kUA/l. Among participants, 21.5% did not develop a reaction, indicating allergy resolution. Approximately 20% of children who develop peanut allergy will outgrow it later in life. Using peanut-specific IgE levels can help

guide which patients with peanut allergy should be considered for a formal oral food challenge. One study showed that 61% of children with levels 5 kUA/l or less, 67% with levels 2 kUA/l or less, and 73% with undetectable peanut-specific IgE passed oral food challenges.[40] Peanut-specific IgE levels below 5 kUA/l may help predict resolution of allergy. Although highly uncommon, peanut allergy may recur after resolution. Fleischer[40] determined that approximately 8% of patients who outgrew their peanut allergy had recurrence of symptoms. This demonstrates the importance of periodic follow-up and re-evaluation of all food allergies, even if believed to have resolved.

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